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Key Words
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Abstract
The challenges faced in developing value-based diagnostics has resulted in few of these tests reaching the clinic, leaving many treatment modalities without matching diagnostics to select patients for particular therapies. Many patients receive therapies from which they are unlikely to benefit, resulting in worse outcomes and wasted health care resources. The paucity of value-based diagnostics is a result of the scientific challenges in developing predictive markers, specifically: (1) complex biology, (2) a limited research infrastructure supporting diagnostic development, and (3) the lack of incentives for diagnostic developers to invest the necessary resources. Better access to biospecimens can address some of these challenges. Methodologies developed to evaluate biomarkers from biospecimens archived from patients enrolled in randomized clinical trials offer the greatest opportunity to develop and validate high-value molecular diagnostics. An alternative opportunity is to access high-quality biospecimens collected from large public and private longitudinal observational cohorts such as the UK Biobank, the US Million Veteran Program, the UK 100,000 Genomes Project, or the French E3N cohort. Value-based diagnostics can be developed to work in a range of samples including blood, serum, plasma, urine, and tumour tissue, and better access to these high-quality biospecimens with clinical data can facilitate biomarker research.

Introduction

Although biomarker studies continue to accumulate in the published literature, few of these biomarkers are being adopted into routine clinical practice, for several

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reasons including the following: (1) insufficient evidence supports their use, (2) the patient population where they are applicable is too small, and (3) there are false discoveries that do not hold up in subsequent testing due to irreproducible assays or a sampling bias [1, 2]. One of the more efficient approaches to avoiding these problems is to conduct studies using biospecimens from previously conducted clinical trials archived under standardized conditions in biobanks. Biomarker studies based on samples from biobanked tissue have been shown to be less expensive to conduct and to provide results sooner than from relying on prospectively collected biosamples [3]. Developing clinically robust biomarkers requires access to the right biospecimens. While this approach offers great promise, identifying high-confidence biomarkers generally requires sufficient samples from at least two independent clinical trial cohorts with similar study designs to be considered level-one evidence of clinical utility [4]. The European Medicines Agency demonstrated one of the first applications of this approach when it approved the use of cetuximab and panitumumab in metastatic colorectal cancer patients with wild-type KRAS tumours. KRAS testing was validated as a companion diagnostic based on biobanked tissue from four randomized clinical trials [5]. Additionally, multiple prospective studies using archived tissue from observational registries can be considered level-two evidence [4, 6–10]. These examples demonstrate how biobanked tissue can greatly facilitate the development and validation of clinically useful biomarkers – and, conversely, how different biospecimen cohorts offer value depending on the clinical setting in which they were collected. As new, more comprehensive analysis technologies such as next-generation sequencing or mass spectrometry protein profiling increase the breadth and depth of interrogation into biological processes, the demand for biological samples to conduct appropriately sized studies will continue to grow.

One case study for successfully validating a molecular diagnostic test using archived samples is the Oncotype® DX Breast Cancer Assay. A recent study published in the *New England Journal of Medicine* described the first results from the TAILORx study, in which patients were prospectively assigned to chemotherapy or hormonal therapy alone based on the Oncotype DX score. This analysis showed that 99.3% of the patients with Oncotype DX assay recurrence scores between 0 and 10, treated with endocrine therapy alone, remained free of distant recurrence at 5 years [11]. This result replicates the results of the original NSABP B-14 validation study that was based on analysing archived fixed tissue samples, where a similar group of patients with the same treatment regimen had a rate of distant recurrence-free survival at 5 years of 98.6% [12, 13].

Optimal Process for Collecting Biospecimens from Studies

The most important criteria for any study biospecimens are that (1) biosamples are collected and stored following high quality standards and consistent protocols that consider the downstream assays and analyses, (2) sufficient clinical data are known to help characterize each patient's disease, (3) metadata describing sample collection, pre-analytical processing, quality control assessment, and the storage method are available, and (4) patients have provided broad informed consent for their tissue to be used for exploratory research beyond the scope of the clinical trial. Since each effort in biomarker development may require specific biospecimen cohorts, providing researchers with the capability to search for appropriate specimen resources available in biobanks can facilitate the successful development of high-value diagnostics helping to advance personalized or precision medicine [14, 15].

Considering the high research value of samples from randomized clinical studies, special attention should be focused on collecting these samples according to standardized procedures and storing them under controlled conditions. The first priority should be securing one-time informed consent from each patient for future biomarker research according to the requirements of each specific jurisdiction. In a high proportion of cases, patients are willing to provide their consent to contributing their biological material and medical data to a biobank as long as they understand the general scope of the research and are properly informed of the risks and benefits of the research. Often patients are not aware of the purpose and existence of biobanks prior to being enrolled in a clinical study. One observational study of 430 cancer patients in Italy found that only 64.5% of the patients were aware of biobanks prior to the study, and the rate was lower among less-educated patients [16]. Therefore, high consent rates are more likely if patients are educated by a health care professional about the benefits their biospecimen donation may bring to medical research. Even clinical studies that involve healthy patients, such as vaccination or screening trials, should prioritize collecting genetic material for biobanking and can achieve a high rate of consent for collecting genetic material for biobanking [17]. It is

key that an appropriate and systematic approach for consenting patients be established to support the collection of biological material, especially in multicentre clinical trials. For biomarker studies from archived biospecimens, it is generally recommended that at least two thirds of the samples be available from the parent study to power the statistical analysis of predictive biomarkers; thus, focusing efforts on obtaining consent from a large fraction of enrolled patients for sample collection and analysis is an important first step [11].

Secondly, establishing appropriate protocols for collecting and storing biological material should be established as part of the study design. Often, financial limitations constrain decisions on which specimens are collected, so investigators should be thoughtful regarding what may be feasible and which samples may provide the highest analytical value for gaining insight into the therapeutic regimen being tested. For example, collecting baseline biospecimens from patients prior to treatment, at various time points throughout the course of treatment, and at disease progression or recurrence provides a longitudinal view of response to the therapy being tested. In the case of metastatic oncologic disease, specimens collected from different anatomical sites may provide insight into disease heterogeneity and resistance to therapy and support the discovery of molecular resistance mechanisms. In addition, a future research benefit may be realized from archived biospecimens carefully collected with control or reference tissue. The biospecimen collection should be included as part of the clinical trial design to ensure that all specimens are collected and quality is controlled and preserved using optimized standard protocols to reduce the impact of pre-analytical factors. Studies have shown that a high degree of concordance between frozen and formalin-fixed paraffin-embedded (FFPE) tissue may be attained for gene expression analyses on common platforms such as oligonucleotide microarrays, next-generation sequencing, PCR product resolution melting analysis for genotyping or copy numbers, real-time RT-PCR, digital PCR, nCounter technology, and DASL bead arrays [18]. While these analytical methods may have been demonstrated to be concordant in the limited number of published studies, these findings often collapse when generalized into high-throughput contract laboratory settings where scale-up factors and specimen variability may impact assay accuracy and lead to false conclusions [14]. Each biomarker assay needs to be validated for the effects of pre-analytical procedures and variability of biosample properties to ensure the reliability of assay results. Ideally, investigators would bank clinical study biomaterials at a central, certified biobank with established, stringent quality control and quality assurance measures. One such measure would be to have a reference panel of biomarkers markers used to monitor the molecular integrity of the biospecimens across their life span [19]. Furthermore, all biospecimens should be linked to the appropriate documentation of relevant quality parameters as well as clinical data in a way that supports research while protecting patient health information.

As biospecimens from clinical trials (especially prospective randomized trials) are extremely precious for future research, proper governance and decision-making should be implemented to ensure that these samples are used for research projects with a high potential for meaningful discovery. Ideally, an independent process should be established to afford a diverse group of investigators the opportunity to request access to banked biospecimens. Improving access to quality-defined biospecimens is a major goal of the European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-ERIC). Therefore, biobanks should be open for external research proposal requests, and the evaluation procedure of such requests should be publicly available as a transparent regulatory document that includes a method for contacting a resource who deals with research requests. Furthermore, the evaluation process should include internal biobank scientists to stimulate cooperation among investigators and maximize the research usability of the biospecimens [20]. Patient organizations or other key stakeholders should be involved in the decision-making process. For example, the Southwestern Oncology Group (SWOG) in the USA invites a broad range of research investigators to submit proposals for consideration, and it evaluates study concepts through a Triage Committee composed of internal and external advisors according to the following criteria [21]: (1) significance of proposed research; (2) expertise of investigator(s); (3) innovation; (4) technical approach, and (5) research environment. Patient organizations for rare diseases, including rare cancers, have proven to be a powerful resource in organizing their member patients to gain a needed critical mass of biospecimen samples to support biomarker research.

Cooperative study groups should be encouraged to support a broad range of research projects while prioritizing the most promising approaches, since the amount of biospecimens from prospective clinical trials is often quite limited. Biomarker investigators should be required to optimize their use of samples to maximize opportunities for further research based on these samples. Similarly,

it should be required that research studies supported by biobank specimens provide open access to the research results generated by the use of human biospecimens [22], although this principle may be limited by the requirement to protect the privacy of sample donors and any restrictions specified in the informed consent forms.

Banking biosamples from population-based cohorts or from patients treated in hospitals holds significant research potential but is infrequently done today. Some countries and regions have centrally organized disease registries with links to biospecimens in biobanks, and these samples may be used to address research questions not feasible to ask from clinical trial samples. For example, elderly patients or women of childbearing age are often excluded from randomized clinical trials, which may cause a major selection bias. Biospecimens from these sources may complement those from clinical trials so that important clinical questions may be asked of a more representative population. The value of these samples can be optimized if the samples and data are collected in a standardized manner. Often, biomarker discovery studies require the biospecimen source to be a homogenous group of patients receiving the same treatments.

One of the best examples of a population-based registry is in Denmark, where a large, comprehensive biobank provides investigators with a valuable research resource. In 1997, the Danish National Pathology Registry (DNPR) initiated a process to allow biospecimens to be used for clinical research, supplying the whole country with a comprehensive resource including a limited number of pathology services and consistent, careful sample handling that reduces the number of sources of bias. All Danish citizens have a unique personal identifier, which can facilitate linking different databases and allows innovative data mining for research studies. Similar to the process mentioned for the SWOG, the Danish National Board of Health has an application process which permits investigators to request use of the data. To access biological specimens, approval is required from the Danish National Committee on Biomedical Research Ethics as well as the local pathology department holding the specimens [23].

Barriers to Implementing a Global Biospecimen Network

There are a growing number of biobanks around the world that actively promote collaboration with investigators; however, several challenges which inhibit clinical investigators from identifying and analysing the right cohorts in the discovery and validation of molecular diagnostics and biomarkers remain. The biggest of these challenges include: (1) access to sufficient data to identify eligible patient cohorts for a study, (2) gaining broad informed consent, (3) normalizing and merging results from biospecimens collected with different methods or under different circumstances, (4) clarifying custodial roles and access rights for banked biospecimens and the matched clinical data, (5) gaining permission to access samples from studies with limited biomaterials, and (6) establishing methods for addressing missing data and metadata [24].

Finding the Right Biospecimens

Since there is no centralized resource describing available biobanked specimen collections, one of the largest challenges for biomarker developers is in finding available patient cohorts to develop and validate biomarkers for a specific clinical use. If investigators do not know a biobank resource that contains the required biospecimens, the most common path biomarker developers follow is to conduct a literature search to find investigators who have conducted studies and banked specimens that may address the required needs. The biomarker developer then contacts these investigators to understand whether these biospecimens are available for new biomarker research. The investigator then must confirm that a sufficient number of specimens with the necessary quality and the appropriate informed consent remain from the original study. Often the attrition rate for these samples is as high as 50% for each round of research analysis [24]. The residual number of eligible samples is often insufficient to support a new biomarker discovery study. In cases where enough appropriate biospecimens are identified, there is typically a long contracting period to gaining access as intellectual property rights, the budget, publication rights, and the future use of the data are negotiated.

Lack of Standardized, Computationally Readable Data Formats and State-of-the-Art Informatics

Conclusions derived from biospecimens are only as good as the quality of the samples that are collected. However, this also applies to the data surrounding the samples. Biobank users have to be able to fully track samples in interoperable electronic systems that pay particular attention to the quality and security of the data. There is an urgent need for stringently standardized data management procedures, computationally readable formats, and commonly shared and accepted terminologies to repre-

sent medical conditions. State-of-the-art, secure data storage as well as high-quality digital curation and annotation of information related to the biosamples are often underappreciated but essential. Not paying attention to downstream interoperability and data integration dramatically diminishes the usefulness of the biosamples and associated data. We currently witness a change in biobanking from locally stored samples and annotation to international, virtual biobank networks. The informatics capability of providing user-friendly, controlled access to samples and data within a harmonized, overarching informatics ecosystem will become one of the key criteria for a well-functioning biobank. There is a need to connect the exploding amount of data to highly automated workflows and data analysis pipelines that provide support for the integration of data from different sources. Artificial intelligence approaches are about to take centre stage in the next years. They all rely on state-of-the-art standards in clinical, genomic, and translational data. These need to be built in from the beginning in the operation of biobanks [25].

Personal Data Protection and Specific Informed Consent Requirements

Establishing the right balance between protecting the privacy of patients and allowing optimal use of biospecimen samples is generally difficult to achieve. For example, some ethics committees may prohibit the use of patient samples for the development of commercial products [26]. While this restriction may appear to some to be reasonable, the goal of most biomarker discovery efforts is meant to lead to commercial tests that will benefit all patients, and therefore this requirement reduces the utility of biospecimens for discoveries that could enhance patient care. Moreover, the refusal of some ethics committees to even ask patients whether or not they are willing to allow such use may be considered disrespectful of patients' autonomy.

Tissue Collection and Management

Some of the biggest challenges limiting biospecimens' utility stem from their considerable heterogeneity. Some biospecimen samples are quite small, some oncology specimens have low fractions of tumour, and often oncology tumour specimens lack a matched normal reference sample. Often standard pre-analytical procedures can markedly impact results or dictate what technologies can be applied to a specimen [27]. Variations can be introduced at many different steps during the collection, preservation, and storage of biospecimen samples. For instance, formaldehyde fixation can cause the biochemical modification of RNA- and DNA-based biomarkers. Tissue fixation time, temperature, and pH have a major impact on chemical modifications and cross-links of DNA or RNA with proteins, which may complicate purification and result in analysis artefacts [28]. In addition to fixation-related effects, RNA profiles in tissues can be altered during processing by gene induction, gene downregulation, and RNA modification and degradation [29]. Standardizing and documenting the whole pre-analytical process of sample management – ranging from collection from the patient [e.g., type of collection device, treatment (medication/surgical procedure)], transport (time and temperature affecting responses to ischemia), processing (e.g., selection of appropriate parts of a tissue), stabilization (fixation in formalin or freezing), and storage to isolation of the various biomolecules – is increasingly recognized as critical to performing reproducible, interpretable research. The European Committee for Standardization (CEN) has recently published technical specifications ('Molecular in-vitro diagnostic examinations – specifications for pre-examination processes') that refer to the existing ISO standard 15189. These technical specifications provide the basis for new ISO standards that are currently under development. An attempt has been made with the Biospecimen Reporting for Improved Study Quality (BRISQ) initiative to enforce the inclusion of a description of the quality of samples used in publications [30]. Under this guideline, reviewers are provided with a list of variables describing the samples used when evaluating publications involving human biomaterials. However, as new insights are gained into how research reproducibility can be affected by pre-analytical biospecimen processing, it is likely that these lists will need to be broadened to keep the literature current on all the artefacts that can affect the interpretation of data published in articles using biospecimens [31].

Control of Samples and Clinical Databases

With each clinical biobank cohort, different rules and kinds of governance may apply as to who has control and the decision-making authority over both the samples and associated clinical data. In some cases, different parties with differing priorities may control the clinical data and the biospecimen samples. For example, a pharmaceutical company may sponsor a clinical trial demonstrating the utility of one drug over another where the biospecimens are collected and managed by a collaborating study group. In this example, the pharmaceutical company may not want to provide access to the clinical data if there is a risk

that further studies may show that only a small proportion of patients benefit from their drug. If the study is not powered to address this question, the result could be a regulatory request for further, expensive clinical trials in defined subpopulations.

Whenever possible, biospecimens should be made available to those researchers who can best maximize the utility of these samples, even if these researchers are in the private sector. Considering the custodianship of samples based on research priority should prevent samples from being imprisoned in silos [32].

Finite Opportunities to Use Well-Characterized Biospecimens

One of the challenges facing those who manage high-value biospecimen collections is deciding which investigators should have access to the resource. This decision is compounded in complexity by dramatic advances in assay technology that permit vast increases in information that can be gained from very limited numbers of specimens. Depending on the biomaterial collected, there may typically be only one or two opportunities to assay these samples in a comprehensive study; therefore, it is wise to be thoughtful when prioritizing research opportunities using these biospecimen resources for a biomedical discovery. Often supplies of certain types of tissue such as serum, plasma, and biopsies are limited; thus, long-term planning is necessary to decide how these resources are most effectively used [33]. It is generally established that developing a predictive marker for the clinic requires that development cohorts be based on randomized trials followed by validation in completely separate clinical cohorts [34]. This creates a dilemma, since typically only one or two prospective randomized clinical trials are conducted for a drug in development. Study designs that make optimal use of these samples should be produced using sound statistical methods. Creative approaches using cohort splitting or other strategies that minimize specimen numbers while maximizing the discovery potential have been devised, although these may, paradoxically, create a suboptimal design for biomarker discovery if the number of markers needed to capture the predictive effect is large and when the biomarker effect sizes are small.

Lack of Longitudinal Data and Sample Collection

As the oncology community gains experience using targeted agents and understanding of the course of disease in patients given these drugs, modes of refractory disease recurrence and drug resistance are emerging. As a result, longitudinal biospecimen collections are increasingly needed for cancer and other chronic diseases. Studies should be designed to take serial biospecimen samples, typically at baseline, at intervals of treatment cycles, and finally at disease progression. These specimens are paired with longitudinal data, allowing investigators to assess the impact of clinical interventions over time and to investigate the mechanisms of disease progression. By testing biospecimen samples collected before and after treatment, insight can be gained into the initial impact of a therapy followed by emergent resistant disease forms. Historically, most clinical study designs collected biospecimens only at a single time point, which generally does not provide the full picture of a patient's disease characteristics and disease course. One of the examples of such a longitudinal biorepository would be the EORTC SPECTA programme [35].

Possible Solutions to Improve the Use of Biospecimens

There are many opportunities for collaboration to improve access to quality-defined biospecimens and the associated clinical information needed for biomarker discovery. Many of these are appearing as new initiatives prospectively collecting samples which will be needed for tomorrow's discoveries. The rate of evolution of knowledge of the best practices for collecting and storing biospecimens has become astonishing. At the same time, new technologies are becoming refined in performance. Molecular profiling can be done on single cells and on highly enriched populations of cells sorted by flow cytometry. This trend tells us that even very small amounts of tissue could become rich sources of discovery, and that every effort should be made to obtain consent and preserve all biospecimens from clinical trials, drug registries, and the like. Ultimately, this material is what enables the transformative discoveries that lead to new therapies. There are also many national and international initiatives which are working to address these challenges and facilitate the harmonization of biobanks, as outlined in table 1.

Opportunities to Improve the Use of Biospecimens

Programmatic and logistic coordination of subject sampling planning is beneficial when multiple studies addressing related scientific questions are being conducted, as this allows direct comparisons of the data and provides the ability to validate findings from one study in the next [36].

Table 1. Organizations and initiatives supporting the harmonization of biobanking infrastructures, standards, and research

Name of organization	Scope	Mission	Website
Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-ERIC)	Europe	BBMRI-ERIC will increase efficacy and excellence of European bio-medical research by facilitating access to quality-defined human health/disease-relevant biological resources through: – the inclusion of associated data in an efficient and ethically and legally compliant manner; – by reducing the fragmentation of the bio-medical research landscape through harmonisation of procedures, implementation of common standards and fostering high-level collaboration; and – by capacity-building in countries with less developed biobanking communities thereby contributing to Europe's cohesion policy and strengthening the ERA	http://bbmri-eric.eu/
Biorepositories and Biospecimen Research Branch (BBRB)	USA	The Biorepositories and Biospecimen Research Branch (BBRB) of the Cancer Diagnosis Program (CDP) provides leadership, tools, resources, and policies in biobanking for the global biomedical research community, to enable translational research and precision medicine for patients. BBRB develops biorepository standards and facilitates Biospecimen Science studies that form the basis of evidence-based practices to guide clinical cancer research and other biomedical studies which utilize biospecimens	http://biospecimens.cancer.gov/default.asp
Canadian Tumour Repository Network	Canada	Vision: to create new opportunities by providing leadership in biobanking to fuel translational cancer research that will improve cancer outcomes in Canada and worldwide Mission: to enhance the capacity and quality of biobanking through standardization and improvement of biobanking processes and frameworks	http://www.ctrnet.ca/
CAP Biorepository Accreditation Program	USA	Accreditation by the College of American Pathologists (CAP) focuses on quality, accuracy, and procedural consistency upon which patient outcomes directly depend. First in the industry to do so, the CAP will now accredit biorepositories, providing you the means to attain and maintain standardization and confidence that you are following best practices	http://www.cap.org/apps/docs/laboratory_accreditation/lap_info/bio_brochure_042011.pdf
French standard NF S96-900: 2011 Quality of Biological Resources	France	NF S96-900: a French national norm, which specifies the requirements for the management system of a Biological Resource Centre (BRC) and the quality of biological resources. Specific evaluation tools are used for this certification	http://www.euroqualitysystem.com/en/our-offers/nf-s96-900/
Human Tissue Authority (HTA)	UK	The HTA is a regulator set up in 2005 following events in the 1990s that revealed a culture in hospitals of removing and retaining human organs and tissue without consent. This organization regulates organisations that remove, store and use human tissue for research, medical treatment, post-mortem examination, education and training, and display in public	http://www.HTA.gov.uk
International Society for Biological and Environmental Repositories (ISBER) Biospecimen Science Working Group	International	ISBER is the only global forum that addresses harmonization of scientific, technical, legal, and ethical issues relevant to repositories of biological and environmental specimens	http://www.isber.org/
NCRI's Confederation of Cancer Biobanks (CCB)	UK	The NCRI's Confederation of Cancer Biobanks (CCB) is a consortium of biobanks and biosample collections based in the UK, established to encourage greater coordination and promote harmonisation between biobanks – enabling them to share best practice and raise awareness of their collections with researchers. There are now over 30 member biobanks and the CCB assists biobank development by providing advice and mutual support	http://ccb.ncri.org.uk/
TuBaFrost (European Human Frozen Tumour Tissue Bank Network) and EurocanPlatform	Europe	EurocanPlatform is a European FP7 project with the aim to set up a European Platform for Translational Cancer Research. Biobanking is one of the Work Packages in the project, where OECI-TuBaFrost was chosen as exchange platform and biobank/sample tracker. Documents were assembled to be used for members in the EurocanPlatform consortium to harmonize and standardize their collections to be used in the platform. […] In the biobanking work package we use the experience of other European biobanking projects to build upon. Work on the future view and opportunities of biobanking. Identify roadblocks and alternative solutions, seeking the cooperation of organisations within EurocanPlatform, ECPC, OECI, ECCO and EORTC. [The main outcomes are published by Riegman et al. [20].]	http://www.tubafrost.org/index.php

Proactive Tissue Collection

There is a common understanding among several groups around the world that there is a distinct need to collect well-characterized biospecimens to support disease treatment research. Many of these initiatives are focused on collecting samples which are intended to answer specific clinical questions or on collecting uniform tissue samples of a specific disease. One of the best examples of this type of programme is the NCI's PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial. In this study, the participants were randomized into two arms: one arm where participants underwent periodic examinations for prostate, lung, colorectal, and ovarian cancer and a control arm receiving usual care from their health care provider. The participants in the intervention arm were asked to provide blood samples at specified time intervals. This approach provided a large repository of serial blood samples from initially healthy people. In addition, this group of researchers collected FFPE tissue from study participants who later developed one of the selected study cancers. Additional study specimens and data were collected on specific subsets of patients. This well-planned and -organized biospecimen repository now has approximately 2.9 million biologic specimens which are available for researchers. This resource has contributed to a large number of research projects, although very few of the study requests for biospecimen access had the objective to develop or validate biomarkers for the early detection of prostate, lung, colorectal, or ovarian cancer. This initiative provides a successful case study, since 'well-documented, standardized guidelines and procedures for each step in the complex workflows of biospecimen collection, processing, storage, requisition, and distribution, as well as data management, were essential for ensuring maximum use of this unique resource for a variety of research studies' [26].

Another area of research which benefits from longitudinal biospecimen collections is that concerned with various brain disorders, as such registries can track disease progression. One of the best examples is from the European Huntington's Disease Network's (EHDN), which is a multilingual, multinational prospective observational study of Huntington's disease in Europe. This registry uses data collection (demographics, phenotype, genotype, medication, comorbidities, and biosamples) which follows a standard protocol across countries. As part of this study, there often are substudies which may focus on particular areas of interest such as a new drug [37]. For example, LEGATO-HD is a phase II double-blind randomized clinical research trial that will look into the safety of an investigational drug called laquinimod and will collect blood samples, offering the potential to develop a companion diagnostic [38]. Besides the EHDN, there are studies working with banked samples that focus on defining biomarkers for other brain disorders; Biomarkers for Alzheimer's and Parkinson's Disease (BIOMARKAPD) is a European multicentre study funded by the EU Joint Programme-Neurodegenerative Disease Research which aims to define biomarkers for the diagnosis and prognosis of Alzheimer's disease and Parkinson's disease [39]. By continuing to fund these types of initiatives, the number of opportunities to identify meaningful biomarkers and therapies to treat various brain disorders will increase.

Evaluating Archived Population-Based Biospecimens with Next-Generation Sequencing

Preliminary studies have demonstrated the utility of archived FFPE samples as a source of DNA for genome-wide sequencing studies, although the age of the samples was found to impact the coverage of the target region in the process used [40]. More studies are needed to better understand the best way to apply new technologies to older stored and preserved biospecimens of varying types. However, the initial results are promising, and recent history indicates a pace of innovation likely to overcome technical barriers to the full genomic and proteomic characterization of most biospecimens, even those of very limited quantity.

Conclusions and Recommendations

One of the key goals in supporting the development of value-based diagnostics is to ensure access to high-quality biospecimens that are harmonized across biobanks [41–43]. This may best be achieved if the following 9 items are dealt with:

1 A simplified, streamlined, and coordinated EU legal framework to stimulate international secondary use of biospecimen research projects
2 Better access to biosamples and data through empowerment of patients, standardized access procedures (e.g., material transfer agreements), and professional governance of biobanks
3 Better standardization of biospecimen quality, with implementation of CEN and ISO standards becoming essential for biomarker development
4 A platform that allows researchers to search and identify biospecimens that are well suited for use in research to develop and validate new value-based diagnostics

5 Biological samples need to be linked to detailed clinical information that includes basic, key data values that are standardized across biobanks and studies
6 The biosamples collected within clinical trials and the scope of consent should allow the samples to be made available for research outside of the scope of clinical trials
7 More emphasis on longitudinally collected samples and clinical data that are available for research
8 Retrospective use of samples collected prior to the introduction of specific consent, including for next-generation sequencing, should be allowed on the basis of Article 32 of the Declaration of Helsinki; specific recommendations should be developed on an international level about how to deal with findings relevant to individual patients in this case
9 Improved benefit for society by open access to research data generated by the analysis of biospecimens

Pilot Projects

As the opportunities and challenges in organizing appropriate biospecimen resources will continue to become more complex, there is an ongoing need to support pilot projects that can be funded by organizations such as the Innovative Medicines Initiative (IMI) and Horizon 2020 and prioritized by the upcoming International Consortium for Personalised Medicine (IC PerMed). The goal would be not to re-create systems but to support increased collaboration among the many valuable programmes that already exist. For example, one work group formed by the NCI proposed developing a pilot study to evaluate the feasibility of combining specimens from suitable studies to better understand the variability across studies [41]. Groups like BBMRI-ERIC are well positioned to coordinate these types of pilot project across the many stakeholders involved in this field to develop a more sustainable and harmonized system of biobanking.

Disclosure Statement

D.S. is an employee of Genomic Health SARL and has received Genomic Health stocks. M.C. is an employee of Celgene Corporation and has received Celgene stocks.

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